

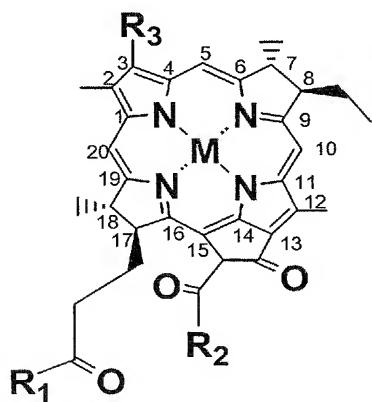
Appln. No. 10/534,692
Amdt. dated January 25, 2010
Reply to Office Action of September 24, 2009

AMENDMENTS TO THE CLAIMS:

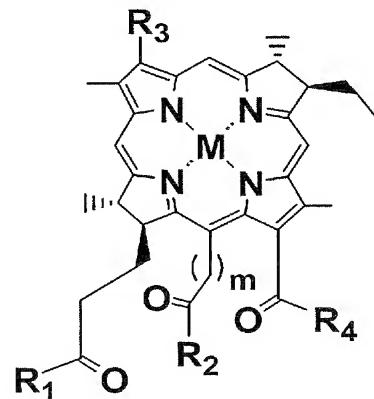
This listing of claims will replace all prior versions, and listings of claims in the application:

Listing of Claims:

1. (Currently Amended) A bacteriochlorophyll derivative compound containing at least one, preferably two or three, negatively charged groups or acidic groups that are converted to negatively charged groups at the physiological pH, of the formula I or II:



(I)



(II)

wherein

M represents 2H or a metal atom selected from the group consisting of divalent Pd, Pt, Co, Sn, Ni, Cu, Zn and Mn, or trivalent Fe, Mn and Cr;

R1, R2, and R4 each independently is Y- R5;

Y is O, S or -NR6;

Appln. No. 10/534,692
Amdt. dated January 25, 2010
Reply to Office Action of September 24, 2009

R₃ is selected from the group consisting of -CH=CH₂, -C(=O)-CH₃, -C(=O)-H, -CH=NR₇, -C(CH₃)=NR₇, -CH₂-OR₇, -CH₂-SR₇, -CH₂-NR₇R'₇, -CH(CH₃)-OR₇, -CH(CH₃)-SR₇, -CH(CH₃)-NR₇R'₇, -CH(CH₃)Hal, -CH₂-Hal, -CH₂-R₇, -CH=CR₇R'₇, -C(CH₃)=CR₇R'₇, -CH=CR₇Hal, -C(CH₃)=CR₇Hal, and -C≡CR₇;

R₅, R₆, R₇ and R'₇ each independently is H or selected from the group consisting of:

(a) C₁-C₂₅ hydrocarbyl optionally containing one or more heteroatoms selected from the group consisting of -O, S and N, carbocyclic or heterocyclic moieties such as pyridyl, and/or optionally substituted by one or more functional groups selected from the group consisting of halogen, oxo, OH, SH, CHO, NH₂, CONH₂, a negatively charged group, and an acidic group that is converted to a negatively charged group at the physiological pH;

(b) a residue of an amino acid, a peptide or of a protein;
and

(c) when Y is O or S, R₅ may further be R₈⁺;

m is 0 or 1; and

R₈⁺ is H⁺ or a cation;

provided that:

(i) at least one of R₅, R₆, R₇ and R'₇ is a hydrocarbon chain as defined in (a) above substituted by a negatively charged group or by an acidic group that is converted to a negatively charged group at the physiological pH; or

(ii) at least one of R_1 , R_2 , and R_4 is OH , SH , $O^-R_8^+$ or $S^-R_8^+$; or

(iii) at least one of R_1 , R_2 , and R_4 is OH , SH , $O^-R_8^+$ or $S^-R_8^+$ and at least one of R_5 , R_6 , R_7 and R'_7 is a hydrocarbon chain substituted by a negatively charged group or by an acidic group that is converted to a negatively charged group at the physiological pH; or

(iv) at least one of R_1 , R_2 , and R_4 is OH , SH , $O^-R_8^+$ or $S^-R_8^+$ and at least one of R_5 , R_6 , R_7 and R'_7 is a residue of an amino acid, a peptide or of a protein; or

(v) at least one of R_5 , R_6 , R_7 and R'_7 is a hydrocarbon chain substituted by a negatively charged group or by an acidic group that is converted to a negatively charged group at the physiological pH and at least one of R_5 , R_6 , R_7 and R'_7 is a residue of an amino acid, a peptide or of a protein;

wherein said negatively charged group is selected from the group consisting of COO^- , COS^- , SO_3^- , and PO_3^{2-} and said acidic group that is converted to a negatively charged group at the physiological pH is selected from the group consisting of $COOH$, $COSH$, SO_3H , and PO_3H_2 ;

but excluding the compounds of formula I wherein M is as defined, R_3 is $-C(=O)CH_3$, R_1 is OH or OR_8^+ and R_2 is $-OCH_3$, and the compound of formula II wherein M is $2H$, R_3 is $-C(=O)CH_3$, R_1 , R_2 and R_4 are OH , and m is 0 or 1.—or both, excluding pentacyclic

Appln. No. 10/534,692
Amdt. dated January 25, 2010
Reply to Office Action of September 24, 2009

~~bacteriochlorophyll derivatives having a free CH₂CH₂COOH or a CH₂CH₂COO⁻ group at position 17, and tetracyclic bacteriochlorophyll derivatives devoid of a central metal atom and having a CH₂CH₂COOH group at position 17, a CH₂COOH or COOH group at position 15, a COOH group at position 13, methyl groups at the positions 2, 7, 12, 18, and ethyl groups at the positions 3 and 8.~~

2. (Currently Amended) A-The bacteriochlorophyll derivative compound according to claim 1 containing two negatively charged groups.

3. (Currently Amended) A-The bacteriochlorophyll derivative compound according to claim 1 containing three negatively charged groups.

4-9. (Cancelled)

10. (Currently Amended) A-The bacteriochlorophyll derivative compound of the formula I or II according to claim 7-1, wherein R₁ is Y- R₅; Y is O, S or NH; and R₅ is a hydrocarbon chain substituted by functional groups selected from of the group consisting of OH, SH, SO₃H, NH₂, CONH₂, COOH, COSH, and PO₃H₂.

11. (Currently Amended) A-The bacteriochlorophyll derivative compound of the formula I or II according to claim 7-1, wherein R₅ is the residue of an amino acid, a peptide or a protein.

12. (Currently Amended) A-The bacteriochlorophyll derivative compound of the formula I or II according to claim 7-1 containing a central Pd metal atom.

13. (Currently Amended) A-The bacteriochlorophyll derivative compound of the formula I according to claim 7-1, wherein:

M is Pd;

R₁ is -NH- (CH₂)_n-SO₃⁻R₈⁺, -NH- (CH₂)_n-COO⁻R₈⁺; -NH- (CH₂)_n-PO₃²⁻ (R₈⁺)₂;

R₂ is methoxy;

R₃ is -C(=O)-CH₃;

R₈⁺ is a monovalent cation such as K⁺, Na⁺, Li⁺, NH₄⁺; and n is an integer from 1 to 10, ~~preferably 2 or 3~~.

14. (Currently Amended) A-The bacteriochlorophyll derivative compound of the formula II according to claim 7-1, wherein:

M represents 2H, divalent Pd, Cu, or Zn or trivalent Mn;

Appln. No. 10/534,692
Amdt. dated January 25, 2010
Reply to Office Action of September 24, 2009

R_1 is $-O^-R_8^+$, $-NH-(CH_2)_n-SO_3^-R_8^+$, $-NH-(CH_2)_n-COO^-R_8^+$ or $-NH-(CH_2)_n-PO_3^{2-}(R_8^+)_2$; or $Y-R_5$ wherein Y is O, S or NH and R_5 is the residue of an amino acid, a peptide or a protein;

R_2 is C_1-C_6 alkoxy, preferably methoxy;

R_3 is $-C(=O)-CH_3$, $-CH=N-(CH_2)_n-SO_3^-R_8^+$; $-CH=N-(CH_2)_n-COO^-R_8^+$; $-CH=N-(CH_2)_n-PO_3^{2-}(R_8^+)_2$; $-CH_2-NH-(CH_2)_n-SO_3^-R_8^+$; $-CH_2-NH-(CH_2)_n-COO^-R_8^+$; or $-CH_2-NH-(CH_2)_n-PO_3^{2-}(R_8^+)_2$;

R_4 is $-NH-(CH_2)_n-SO_3^-R_8^+$; $-NH-(CH_2)_n-COO^-R_8^+$; or $-NH-(CH_2)_n-PO_3^{2-}(R_8^+)_2$;

R_8^+ is a monovalent cation, preferably K^+ ; and

m is 1, and n is an integer from 1 to 10, preferably 2 or 3.

15. (Currently Amended) A-The bacteriochlorophyll derivative compound of formula II in claim 7 1 wherein:

M is divalent Pd;

R_1 is $-O^-R_8^+$, $-NH-(CH_2)_n-SO_3^-R_8^+$, or $Y-R_5$ wherein Y is O, S or NH and R_5 is the residue of an amino acid, a peptide or a protein;

R_2 is C_1-C_6 alkoxy, preferably methoxy;

R_3 is $-C(=O)-CH_3$, $-CH=N-(CH_2)_n-SO_3^-R_8^+$; or $-CH_2-NH-(CH_2)_n-SO_3^-R_8^+$;

R_4 is $-NH-(CH_2)_n-SO_3^-R_8^+$; $NH-(CH_2)_n-COO^-R_8^+$; or $NH-(CH_2)_n-PO_3^{2-}(R_8^+)_2$;

R_8^+ is a monovalent cation, preferably K^+ ;

m is 1, and n is 2 or 3.

16. (Currently Amended) A-The bacteriochlorophyll derivative compound of the formula I according to claim 13, consisting of the compound Palladium bacteriopheophorbide a 17³-(3-sulfopropyl) amide potassium salt.

17. (Currently Amended) A-The bacteriochlorophyll derivative compound of the formula II according to claim 15, selected from the group consisting of:

Palladium 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(2-sulfoethyl) amide dipotassium salt; 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(2-sulfoethyl) amide dipotassium salt;

Palladium 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹, 17³-di(3-sulfopropyl) amide dipotassium salt;

Palladium 3¹-(3-sulfopropylimino)-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹, 17³-di(3-sulfopropyl) amide tripotassium salt;

Copper(II) 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(2-sulfoethyl) amide dipotassium salt;

Zinc 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(2-sulfoethyl) amide dipotassium salt;

Appln. No. 10/534,692
Amdt. dated January 25, 2010
Reply to Office Action of September 24, 2009

Manganese (III) 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(2-sulfoethyl) amide dipotassium salt;
Palladium 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(2-sulfoethyl) amide, 17³-(N-immunoglobulin G) amide potassium salt;
Palladium 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(2-carboxy-ethyl) amide dipotassium salt;
Palladium 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(3-phosphopropyl) amide tripotassium salt; and
Palladium 3¹-(3-sulfopropylamino)-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹,17³-di(3-sulfopropyl) amide tripotassium salt.

18. (Original) Palladium 3¹-oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13¹-(2-sulfoethyl) amide dipotassium salt.

19. (Currently Amended) A pharmaceutical composition comprising a—the bacteriochlorophyll derivative compound according to claim 1, and a pharmaceutically acceptable carrier.

20-35. (Cancelled)

36. (Currently Amended) A method for vascular-targeted
tumor photodynamic therapy (VTP), which comprises:

- (a) administering to an individual in need a-the
bacteriochlorophyll compound according to claim 1; and
- (b) irradiating the local area of the tumor.

37. (Currently Amended) A method for photodynamic
therapy of age-related macular degeneration by vascular
occlusion, which comprises:

- (a) administering to an individual in need a-the
bacteriochlorophyll compound according to claim 1; and
- (b) irradiating the local area of the macular degeneration.

38. (Currently Amended) A method for tumor diagnosis
which comprises:

- (a) administering to a subject suspected of having a tumor,
a-the bacteriochlorophyll compound according to claim 1; and
- (b) irradiating the subject by standard procedures and
measuring the fluorescence of the suspected area, wherein a
higher fluorescence indicates tumor sites.

39-41 (Cancelled).

42. (Currently Amended) The A compound Palladium bacteriopheophorbide a 17^3 -(3-sulfo-1-oxysuccinimide) ester sodium salt, ~~as an intermediate.~~

43. (Currently Amended) A method for the preparation of compounds of formula II ~~in~~of claim 7 1, wherein R_1 is $-O^- R_8^+$; R_2 is $-OCH_3$; R_3 is acetyl; R_4 is a group $-NH-(CH_2)_n-SO_3^- R_8^+$; R_8^+ is a monovalent cation; m is 1 and n is 1 to 10, which comprises:

- (i) reacting the corresponding M-bacteriopheophorbide of formula I, wherein R_1 is OH with an aminosulfonic acid of the formula $H_2N-(CH_2)_n-SO_3H$ in a R_8^+ -buffer; and
- (ii) isolating the desired compound of formula II.

44. (Currently Amended) The method according to claim 43 for preparation of palladium 3^1 -oxo-15-methoxycarbonylmethyl-rhodobacteriochlorin 13^1 -(2-sulfoethyl) amide dipotassium salt, which comprises: (i) reacting Pd-bacteriopheophorbide a with taurine of the formula $H_2N-(CH_2)_2-SO_3H$ in a K^+ -buffer; and (ii) isolating the ~~title~~-compound.

45. (Currently Amended) A method for the preparation of compounds of formula II in claim 7 1, wherein R_1 is $-O^- R_8^+$; R_2 is $-OCH_3$; R_3 is acetyl; R_4 is a group $-NH-(CH_2)_n-COO^- R_8^+$; R_8^+ is a monovalent cation; m is 1 and n is 1 to 10, which comprises:

- (i) reacting the corresponding M-bacteriopheophorbide of formula I wherein R₁ is OH with an aminocarboxylic acid of the formula H₂N-(CH₂)_n-COOH in a R₈⁺-buffer; and
- (ii) isolating the desired compound of formula II.

46. (Currently Amended) A method for the preparation of compounds of formula II in claim 7 1, wherein R₁ is -O⁻ R₈⁺; R₂ is -OCH₃; R₃ is acetyl; R₄ is a group -NH-(CH₂)_n-PO₃²⁻ (R₈⁺)₂; R₈⁺ is a monovalent cation; m is 1 and n is 1 to 10, which comprises:

- (i) reacting the corresponding M-bacteriopheophorbide of formula I wherein R₁ is OH with an aminophosphonic acid of the formula H₂N-(CH₂)_n-PO₃H₂ in a R₈-buffer; and
- (ii) isolating the desired compound of formula II.

47. (Currently Amended) A method for the preparation of compounds of formula II in claim 7 1, wherein R₁ and R₄ contain the same negatively charged group, which comprises:

- (i) reacting the corresponding M-bacteriopheophorbide with an excess of the aminosulfonic, aminocarboxylic or aminophosphonic acid in a R₈⁺-buffer; and
- (ii) isolating the desired 13,17-disubstituted derivative compound of formula II.

48. (Currently Amended) A method for the preparation of compounds of formula II in claim 7 1, wherein R₁ and R₄ are each a group -NH- (CH₂)_n-SO₃⁻R₈⁺; R₂ is -OCH₃; R₃ is acetyl; R₈⁺ is a monovalent cation; m is 1 and n is 1 to 10, which comprises:

(i) coupling the corresponding M-bacteriopheophorbide of formula I wherein R₁ is OH with N-hydroxy-sulfosuccinimide (sulfo NHS) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC);

(ii) reacting the resulting M-bacteriopheophorbide-17³-N-hydroxy-sulfosuccinimide ester with an excess of an aminosulfonic acid of the formula H₂N- (CH₂)_n-SO₃H in a R₈⁺-buffer, thus obtaining a compound of formula I having a sole negatively charged group at position 17;

(iii) reacting the product of step (ii) with an excess of H₂N- (CH₂)_n-SO₃H in a R₈⁺-buffer; and

(iv) isolating the desired compound of formula II.

49. (Currently Amended) A method for the preparation of compounds of formula II in claim 7 1, wherein R₁ and R₄ are each a group -NH- (CH₂)_n-COO⁻R₈⁺; R₂ is -OCH₃; R₃ is acetyl; R₈⁺ is a monovalent cation; m is 1 and n is 1 to 10, which comprises:

(i) coupling the corresponding M-bacteriopheophorbide of formula I wherein R₁ is OH with N-hydroxy-sulfosuccinimide (sulfo

Appln. No. 10/534,692
Amdt. dated January 25, 2010
Reply to Office Action of September 24, 2009

NHS) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC);

(ii) reacting the resulting M-bacteriopheophorbide-17³-N-hydroxy-sulfosuccinimide ester with an excess of an aminocarboxylic acid of the formula $H_2N-(CH_2)_n-COOH$ in a R_8^+ -buffer, thus obtaining a compound of formula I having a sole negatively charged group at position 17;

(iii) reacting the product of step (ii) with an excess of $H_2N-(CH_2)_n-COOH$ in a R_8^+ -buffer; and (iv) isolating the desired compound of formula II.

50. (Currently Amended) A method for the preparation of compounds of formula II in claim 7 1, wherein R_1 and R_4 are each a group $-NH-(CH_2)_n-PO_3^{2-} R_8^+$; R_2 is $-OCH_3$; R_3 is acetyl; R_8^+ is a monovalent cation; m is 1 and n is 1 to 10, which comprises:

(i) coupling the corresponding M-bacteriopheophorbide of formula I wherein R_1 is OH with N-hydroxy-sulfosuccinimide (sulfo NHS) in the presence of 1-ethyl-3-(3-dimethylaminopropyl)-carbodiimide (EDC);

(ii) reacting the resulting M-bacteriopheophorbide-17³-N-hydroxy-sulfosuccinimide ester with an excess of an aminophosphonic acid of the formula $H_2N-(CH_2)_n-PO_3H_2$ in a R_8^+ -buffer, thus obtaining a compound of formula I having a sole negatively charged group at position 17;

Appln. No. 10/534,692
Amdt. dated January 25, 2010
Reply to Office Action of September 24, 2009

(iii) reacting the product of step (ii) with an excess of $\text{H}_2\text{N}-\text{(CH}_2\text{)}_n-\text{PO}_3\text{H}_2$ in a R_8^+ -buffer; and (iv) isolating the desired compound of formula II.